

**CLAIMS:**

- 5 1- A method to achieve MHC-class II mediated immunomodulation in a mammal in need of such treatment, which comprises administering to the mammal at least one statin, or a functionally or structurally equivalent molecule, in an amount effective to modulate MHC class II expression in the mammal.
- 10 2- A method to achieve MHC-class II mediated immunosuppression in a mammal in need of such treatment, which comprises administering to the mammal at least one statin, or a functionally or structurally equivalent molecule, in an amount effective to suppress MHC class II expression in the mammal.
- 15 3- A method to achieve MHC-class II mediated anti-inflammatory effect in a mammal in need of such treatment, which comprises administering to the mammal at least one statin, or a functionally or structurally equivalent molecule, in an amount effective to suppress MHC class II expression in the mammal.
- 4- A method to achieve CD40-mediated anti immuno-inflammatory effect in a mammal in need of such treatment, which comprises administering to the mammal at least one statin, or a functionally or structurally equivalent molecule, in an amount effective to modulate CD40 expression.
- 20 5- The method of any one of claims 1 to 4, wherein said mammal is a human.
- 6- The method of any one of claims 1 to 4, wherein said mammal does not suffer from hypercholesterolaemia.
- 7- The method of claims 1, 2 or 3, wherein said amount is effective to specifically modulate IFN- $\gamma$  inducible MHC class II expression.
- 8- The method of claim 4, wherein said amount is effective to specifically modulate inducible CD40 expression.
- 25 9- The method of claim 8, wherein said inducible CD40 expression is induced by IFN- $\gamma$ .

10- The method of claims 1, 2 or 3, wherein said mammal is suffering from a condition which involves IFN- $\gamma$  inducible CITA expression.

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A2 11- The method of any one of claims 1 to 4, wherein said mammal is suffering from a condition which is an autoimmune disease.

5 12- The method of claim 11, wherein said autoimmune disease is type I diabetes, multiple sclerosis, rheumatoid arthritis, Crohne's disease or lupus erythematosus.

13- The method of any one of claims 1 to 4, wherein said mammal is under treatment in preparation of or after an organ or tissue transplantation.

10 14- The method of any one of claims 1 to 4, wherein said mammal is under treatment in preparation of an organ or tissue transplantation.

15- The method of any one of claims 1 to 4, wherein said mammal is suffering from a condition which is psoriasis or inflammation.

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A3 16- The method of any one of claims 1 to 4, wherein said statin is used in a topical application.

17- The method according to claim 16, wherein said topical application is on dermis or eye.

15 18- The method of any one of claims 1 to 4, wherein said statin is Compactin, Atorvastatin, Lovastatin, Pravastatin, Fluvastatin, Mevastatin, Cerivastatin, Rosuvastatin or Simvastatin.

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A4 19- The method of any one of claims 1 to 4, wherein said statin is Atorvastatin.

20- The method of any one of claims 1 to 4, wherein said statin, or said functionally or structurally equivalent molecule, has no lipid-lowering effect.

20 21- The method of any one of claims 1 to 4, wherein the statin, or a functionally or structurally equivalent molecule, is administered in the absence of any other immunosuppressive agents.

22- The method of any one of claims 1 to 4, wherein said amount is comprised between 10 and 80 mg per day.

23- The method of any one of claims 1 to 4, wherein said amount is comprised between 20 and 40 mg per day.

24- The method of any one of claims 1 to 4, wherein said administration comprises intralesional, intraperitoneal, intramuscular or intravenous injection; infusion; or topical, nasal, oral, ocular or otic delivery.

25- The method of any one of claims 1 to 4, wherein said administration is made daily.

26- The method of any one of claims 2 to 4, wherein the immunosuppression or anti-inflammatory effect is the result of repression of T lymphocyte activation.

27- A method for identifying molecules that inhibit IFN- $\gamma$  induced CIITA expression, said inhibition being at least partially reversible by addition of L-mevalonate, comprising the steps of:

- contacting a cell which is IFN- $\gamma$  responsive with a candidate inhibitory molecule and with IFN- $\gamma$ ;

- detecting the inhibition or absence of CIITA expression or MHC class II expression in the presence of the candidate molecule;

- further contacting the cell with L-mevalonate; and

- detecting a total or partial reversal of the inhibitory effect.

28- A method for identifying molecules that inhibit IFN- $\gamma$  induced CIITA expression, comprising the steps of:

- contacting a cell which is IFN- $\gamma$  responsive with a statin, or a functional or structural equivalent thereof, and with IFN- $\gamma$ ;

- detecting the inhibition or absence of CIITA expression or MHC class II expression in the presence of the statin, or the functional or structural equivalent thereof.

29- A method for identifying molecules that inhibit induced CD40 expression, said inhibition being at least partially reversible by addition of L-mevalonate, comprising the steps of:

-contacting a cell with a candidate inhibitory molecule and with the molecule inducing CD40 expression;

5 -detecting the inhibition of CD40 expression in the presence of the candidate molecule;

-further contacting the cell with L-mevalonate; and

-detecting a total or partial reversal of the inhibitory effect.

30- A method according to claim 29, wherein said molecule inducing CD40 expression is IFN- $\gamma$ .

10 31- A method of treating a patient afflicted with an autoimmune disease, comprising administering to said patient a compound that inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in an amount effective to treat said disease.

32- The method of claim 32 wherein said compound has a therapeutically insignificant lipid-lowering effect and suppresses MHC Class II expression.

15 33- A method of treating a patient suffering from an autoimmune disease or condition comprising:

administering to said patient at least one compound, capable of measurable HMG-CoA reductase inhibition and inhibition of MHC Class II expression in said patient, in an amount effective to treat such autoimmune disease or condition.

20 34- A method of treating a patient in preparation for or after an organ tissue transplant comprising:

administering to said patient at least one compound capable of measurable HMG-CoA reductase inhibition and inhibition of MHC Class II expression in said patient, in an amount which is effective to prevent tissue rejection.

25 35- A method of preventing or treating tissue or organ rejection in a patient comprising administering to said patient a compound that inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) in an amount effective to prevent or treat tissue or organ rejection.

36- A method of treating an autoimmune disease or an immuno-inflammatory disease, comprising administration of at least one statin, or a functionally or structurally equivalent molecule, to a subject in an amount effective to modulate IFN- $\gamma$  inducible MHC class II expression and / or CD40 expression in the subject, such that the symptoms of said disease are at least partially alleviated.

37- A method according to claim 36, wherein the disease is rheumatoid arthritis.

38- The method of claim 36, wherein said subject does not suffer from hypercholesterolemia.

39- The method of claim 36, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.

40- The method of claim 36, wherein said statin is administered in conjunction with another rheumatoid arthritis therapy.

41- The method of claim 40, wherein said other rheumatoid arthritis therapy is selected from the group consisting of steroids; nonsteroidal anti-inflammatory agents; (NSAIDs); disease modifying anti-rheumatoid drugs (DMARDs); and combinations thereof.

42- The method of claim 41, wherein said nonsteroidal anti-inflammatory agent is selected from the group consisting of salicylates; fenoprofen; naproxen; piroxicam; tolmetin; indomethacin; sulindac; meclofenamate; and combinations thereof.

43- The method of claim 41, wherein said disease modifying anti-rheumatoid drug is selected from the group consisting of D-penicillamine; gold salts (both parenteral and oral forms); hydroxychloroquine; azathioprine; methotrexate; cyclophosphamide; and combinations thereof.

44- The method of claim 36, wherein said statin or functionally or structurally equivalent molecule, is administered orally.

45- The method of claim 36, wherein said amount is at least from about 10 and 80mg/day.

46- The method of claim 36, wherein said amount is at least from about 20 and 40mg/day.

47- Use of a statin or a functionally or structurally equivalent molecule, for the preparation of a medicament for treating an autoimmune disease or an immuno-inflammatory disease, such statin being present in an amount effective modulate IFN- $\gamma$  inducible MHC class II expression and / or CD40 expression, thereby alleviating at least partially the symptoms of said disease.

48- Use according to claim 47 wherein the disease is rheumatoid arthritis.

49- A method of preventing or treating tissue rejection in a subject comprising administering to said subject at least one statin or a functionally or structurally equivalent molecule in an amount which is effective to inhibit IFN- $\gamma$  inducible MHC Class II expression and /or CD40 expression such that rejection is at least partially prevented or treated.

50- A method of treating a tissue graft prior to, during or after transplantation, comprising administering to a patient a statin or a functionally or structurally equivalent molecule, in an amount which is effective to inhibit IFN- $\gamma$  inducible MHC Class II expression and /or CD40 expression effective such that inflammation or tissue rejection, or both, is reduced.

15 51- The method of claim 50, wherein said tissue graft is selected from the group consisting of skin; bone; abdominal wall; pericardium; periosteum; perichondrium; intervertebral disc; articular cartilage; dermis; epidermis; ligaments; bowel and tendons.

52- The method of claim 50, wherein said tissue graft is selected from the group consisting of living and synthetic graft materials.

20 53-The method of claim 50, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.

54- The method of claim 50, wherein the tissue graft is a skin graft.

55- The method of claim 54 wherein the skin graft is used for the treatment of skin ulcers.

25 56- The method of claim 55, wherein the skin graft is a skin allograft.

57- The method of claim 50, wherein the statin or a functionally or structurally equivalent molecule, is administered orally or topically.

58- The method of claim 50, wherein said amount is at least from about 10 and 80mg/day.

59- The method of claim 50, wherein said amount is at least from about 20 and 40mg/day.

5 60- Use of a statin or a functionally or structurally equivalent molecule in the preparation of a medicament for reducing inflammation or for reducing tissue rejection, or both, such statin being present in an amount effective to inhibit IFN- $\gamma$  inducible MHC Class II expression and /or CD40 expression such that inflammation or tissue rejection, or both, is reduced, for administration to a subject before, during or after a tissue graft.

10 61- The use of claim 60, wherein said tissue graft is a skin graft.

62- The use of claim 60, wherein said administration of said statin does not include administration of other immunosuppressive agents.

15 63- The use of claim 60, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.

64- A kit comprising a tissue graft material and a statin, or a functionally or structurally equivalent molecule, either in the same or separate packaging.

65- The kit of claim 64, wherein said tissue graft material is a natural or engineered material.

20 66- The kit of claim 65, wherein said tissue graft material is selected from the group consisting of skin; bone; abdominal wall; pericardium; periosteum; perichondrium; intervertebral disc; articular cartilage; dermis; epidermis; bowel; ligaments; and tendons.

67- The kit of claim 64, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.

- 5 68- A method of preventing or treating organ rejection in a subject comprising administering to said subject prior to or during transplantation, at least one statin or a functionally or structurally equivalent molecule, in an amount which is effective to inhibit IFN- $\gamma$  inducible MHC Class II expression and /or CD40 expression such that rejection is at least partially prevented or treated.
- 69- The method of claim 68, wherein said organ is selected from the group consisting of heart, kidney, and liver.
- 10 70- The method of claim 68, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.
- 71- The method of claim 68 wherein the organ is heart and the statin or functionally or structurally equivalent molecule, is administered to the subject prior to the transplantation.
- 72- The method of claim 68 wherein the organ is kidney and the statin or functionally or structurally equivalent molecule, is administered to the subject prior to the transplantation.
- 15 73- The method of claim 68, wherein the statin or functionally or structurally equivalent molecule, is administered by oral intralesional, intraperitoneal, intramuscular delivery or by intravenous injection.
- 74- The method of claim 68, wherein said amount is at least from about 10 and 80mg/day.
- 75- The method of claim 68, wherein said amount is at least from about 20 and 40mg/day.
- 20 76- A method of treating an inflammatory disorder comprising administering to a subject, at least one statin or a functionally or structurally equivalent molecule, in an amount which is effective to inhibit IFN- $\gamma$  inducible MHC Class II expression and /or CD40 expression such that inflammation is reduced.
- 25 77- The method according to claim 76, wherein the inflammatory disorder is selected from the group consisting of inflammatory skin disease, inflammatory ocular disorder, and lupus erythematosus.



78- A method according to claim 76 wherein the inflammatory disorder is an inflammatory skin disorder.

79- The method of claim 76, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.

80- The method of claim 76 wherein the statin is administered orally or topically.

81- The method of claim 76 wherein the statin is administered topically as a gel, cream, spray, or powder.

82- The method of claim 76 wherein the inflammatory skin disease is selected from the group consisting of psoriasis and eczema.

83- The method of claim 76, wherein said amount is at least from about 10 and 80mg/day.

84- The method of claim 76, wherein said amount is at least from about 20 and 40mg/day.

85- Use of a statin or a functionally or structurally equivalent molecule in the preparation of a medicament for reducing inflammation in an inflammatory skin disorder, such statin being present in an amount effective for reducing inflammation.

86- A method according to claim 76 wherein the inflammatory disorder is an inflammatory ocular disorder.

87- The method of claim 86, wherein said statin is selected from the group consisting of compactin; atorvastatin; lovastatin; pravastatin; fluvastatin; mevastatin; cerivastatin; rosuvastatin and simvastatin; and combinations thereof.

88- The method of claim 86 wherein the statin is administered orally or topically.

89- The method of claim 86 wherein the statin is administered topically as a gel, cream, spray, or powder.

90- The method of claim 86 wherein the ocular disease is uveitis.

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